

Urogenital and anal chlamydia trachomatis and human papillomavirus infections

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Valorisation

Valorisation

The social and economic relevance of the research results

The main focus of the thesis are most commonly diagnosed worldwide bacterial and viral sexually transmitted infections (STI), namely *Chlamydia trachomatis* (Ct) and human papillomavirus (HPV). Among long term complications of Ct are pelvic inflammatory disease, ectopic pregnancy, infertility, and ocular and respiratory infections in newborns. Persistent infection with HPV is a necessary cause of most of cervical and anal cancers, some cancers of the vagina, vulva, penis, rectum, oropharynx, head and neck, as well as skin and genital warts. In addition, both infections can facilitate HIV transmission. Although the two STIs are major health problems, causing serious morbidity and mortality, estimates of the global prevalence and incidence of both Chlamydia and HPV infections are limited by quantity and quality of data available from the different regions of the world due to the nature of the pathogens or the lack of reliable information from many world areas, as a result of the variety of surveillance systems or approaching high-risk populations (i.e., the presence of stigma). This also applies to such country as the Russian Federation, which originally centralized around clinical dermatovenereology services model of STI control faced tremendous challenges during the last decades caused by an abrupt free-market transition in the 1990's followed by socio-political and economic changes that contributed to rocketing of the burden of STI, including HIV. In addition, the scarce funding for health care and its management resulted in limited research studies on STIs in the country.

Addressing the burden of STIs is important in efforts to achieve the health ambitions of the Sustainable Development Goals, as embodied in the global health sector strategy on STI 2016-2021 which was adopted by the 69th World Health Assembly of the World Health Organization in May 2016.

This work starts with the stocktake of all available data on the prevalence of genital Ct infections in all available peer reviewed studies for Russian populations. This analysis was additionally expanded with data from the multicenter study run in the second-largest Russian city of St. Petersburg among 1263 people whose urethral, anal, cervical, and prostate samples were tested for the presence of Ct DNA in St. Petersburg and in Amsterdam. The study (**Chapter 2**) revealed that the overall prevalence of genital Ct infections across different Russian populations may range from 2.9% to 33%. The

multicenter study specified the risk factors, which included being symptomatic (observed in particular among men), being younger than 30 years, and being a man who has sex with men (MSM). The initiation of screening programmes for Ct infections applied to high-risk populations (i.e., young people, women and men with multiple partners, MSM, commercial sex workers, drug users) in Russia was suggested to be considered. As Ct detection with Russian tests in some settings in St. Petersburg yielded levels of reliability comparable with internationally available tests, such screening programmes could rely on less costly locally manufactured tests, though if quality of sampling and testing will remain sustainable only. Currently, testing for Ct in Russia is obligated among some population groups such as pregnant women, gynaecological or venerological patients and men with urogenital symptoms. The deployment of screening programmes for Ct targeting high-risk group populations would bring additional benefits to the Russian health care system and patients. This will result in earlier detection and treatment of Ct, reduction in transmission of other STI, including HIV, and, also, decrease in Chlamydia-related long term complications across the nation. It will further help in evaluation the real incidence of STI, antibiotic resistance, and molecular epidemiology. All of these would result in reducing the costs for the country's health care system.

The observed geographic variations in Chlamydia serovar (**Chapter 3**) and strain types (**Chapter 4**) distribution between Russia and other geographic regions, due to potential selective mixing and adaptive diversification, supports further studies that employ extended numbers of isolates among cohorts with different risk profiles for infections and with the spread of different variants of Chlamydia. This approach could result in establishment of biobanks of Ct/STI samples. Such studies will be of great value as they could help to explain differences in Ct and STI prevalence at a population level and could provide useful insight into microbiological characteristics of infection (e.g. concurrence of infection, bacterial load, and resistance patterns), molecular epidemiology and transmission which all are essential for developing prevention strategies, especially given the increasing globally number of cross-border trips, migration and expanding international sexual networks.

Importantly, current medical practice worldwide does not always facilitate discussion of sexual behaviours and MSM may face different barriers that do not experience many of heterosexual men. Among them, but not limited to, are the lack of welcoming clinical environment and adequate health insurance (e.g., no health insurance through the

spouse's employer as same-sex marriage currently is not an option in many countries). Conducting a study presented in **Chapter 5**, on evaluation of the microbial cure of Chlamydia LGV and non-LGV with doxycycline treatment by testing for Ct DNA and RNA persistence in Dutch MSM anal swab specimens, is difficult or even impossible in countries where MSM are less visible, as a result of the social stigma or religious laws that strictly prohibit homosexuality. *A joint approach with political, including social and economic, commitment to reduce stigma is of great relevance.* From a public health perspective, stigma is important because it contributes to delays in seeking treatment, and, therefore, increased risk of STI transmission. The lack of stigma will help to better identify risk factors and detect an infectious agent. Conducting such a study in the Netherlands allowed properly to identify the risk factors (MSM and HIV-positivity), detect an infectious agent (Ct LGV vs non-LGV strains) and result in the support to develop international recommendations on extended treatment regimen for LGV (21-days) versus non-LGV (7-day) Ct proctitis.

Studies of the epidemiology of HPV infection in men are essential. *Understanding HPV natural history and transmission dynamics will lead towards improvements in cancer control through optimal uses of HPV vaccines in both women and men.* The thesis broadens knowledge on the natural history of mucosal and cutaneous HPV infections and evaluates epidemiological and diagnostic aspects of oncogenic and cutaneous HPVs in men in particular.

Expressed prostate secretion (EPS) samples represent additional informative and relatively easy to obtain sampling material for the studies on urogenital infections. Interestingly, Chlamydia prevalence was found higher in the groups where urethral samples were pooled with EPS samples (**Chapter 2**). Combining urethral and EPS samples resulted in the 42.0% high-risk HPV-positivity in the studied population the majority of which was represented by HIV-negative men who have sex with women (MSW) (**Chapter 6**), almost twice as much as seen when analysing only samples from the distal urethra. EPS tested alone or in a combination with urethral swabs might not provide the complete picture but undoubtedly improve our understanding of abundance of genital microbiota. Obtained findings support further studies to elucidate whether the shift in microbiome (prostate or genital) could be involved in cancerogenesis, i.e. by applying the samples obtained in men preceding the diagnosis of urogenital (prostate) and anal cancers. Contrary to the prostate tissue that requires performing the prostate biopsy, EPS is

relatively easy (and not-expensive) to obtain at the time of routine urological examination. In addition, because of the presence of EPS in the ejaculate, the study of EPS is of particular interest in studies of the transmission of infections to the sexual partner(s).

The data on HPV prevalence in heterosexual males worldwide are scarce. The thesis broadens knowledge on the prevalence and the determinants of presence for a broad range of cutaneous β , γ (**Chapter 7**) and mucosal α (**Chapter 8**) HPV types in the anal canal of men, in which MSM and MSW were recruited from the same population, using a Luminex technology. *Knowledge on HPV epidemiology obtained in diverse male populations is essential for a better understanding of transmission to sexual partners and the role of different HPVs as co-factors in the anogenital carcinogenesis.* Sexual orientation and HIV status were major determinants of anal presence for all three HPV genera but anal cutaneous and mucosal HPVs were commonly found among the studied Russian heterosexual men (24%, 14% and 15.7% for β -, γ - and α -HPVs, respectively). The routes for the transmission of HPVs into the anal canal in MSW remain unclear. Although the presence of HPV DNA may not necessarily indicate presence of infectious virus, the obtained findings posit that routes other than penile-anal intercourse may be important in HPV transmission. Also, the studied MSW population does not represent the general population but HPV is known to be associated with a variety of cancers in men, including anal cancer and a subset a subset of penile and oral cancer, which incidence has been increasing during the last decades. *The gender-neutral HPV routine vaccination could be recommended to be introduced as a part of cancer prevention strategy.* Such vaccination may prevent genital warts and the spread of HPV to sexual partners through the herd immunity.

The international cooperation and knowledge transfer is of great importance for public health worldwide. During the last few decades much progress has been made in the management of several STIs, including Chlamydia and HPV infections, globally. The thesis provides an insight that such progress would be impossible without the knowledge transfer provided by the leading state-of-art centres located mostly in high-income countries to low- and middle-income countries (LMICs), which results in the development and spread of technically advanced facilities in LMICs and save many human lives across the globe.

Target groups

This work contains useful information and specific recommendations for the evaluation of the current STI control strategies with a focus on low-resource settings. In addition to new scientific knowledge such as the first overview of data on the prevalence of Ct in Russia, first data on Ct serotypes, serogroups and strains in Russia, evidence for the microbiological cure of Ct LGV and non-LGV proctitis, first data on the role of prostate secretion in the studies on HPV epidemiology in men, first data on the distribution of anal cutaneous β - and γ -HPVs and data on prevalence and the determinants of the presence for mucosal and cutaneous HPVs in the anal canal in HIV-negative heterosexual men (with a potential role of auto-inoculation), this thesis provides essential information for healthcare in general and for society, both in Russia and worldwide. The ongoing transmission of Ct, HPV and other STI, including HIV transmission as a result of high risk behaviour and the weakness of existing STI control, and low performance of cancer prevention and control management, including the lack of organized cervical cancer screening and HPV vaccination programmes is a challenge which need individual, national, and global attention and commitment.

Population of reproductive age

First, the results of this thesis are of importance for the whole sexual active population in Russia and in other low- and middle-income resource settings. Individuals of reproductive age should be aware of the common occurrence of genital and anal infections, their long term complications, and potential role in HIV transmission. Moreover, they should be aware of common high risk behaviour as described in the current thesis.

National policy makers

Second, policy makers on the federal (Ministry of Health) and regional (republican, provincial and territorial ministries of health) levels are a target. The advantages and challenges in the current STI and cancer control strategies should be regularly evaluated and updated, to better design and implementation of adjusted STI and cancer control strategies. The current best practice guidelines on STI and cancer control should be applied according to the regional situation. A joint approach with political, including social and economic, commitment is needed to reduce stigma across the nation.

Products, services and activities

The industry

Third, the results of this thesis should be interesting for the pharmaceutical and biotechnological industry, both Russian and global players. The high prevalence of bacterial STI, including Ct, among some populations requires the introduction of effective and not costly antibiotics to the market as well as proper control on antibacterial resistance. The high prevalence of STI, including HIV, among some populations, in particular among high-risk and/or stigmatized, could pave the way for the development and introduction of point-of-care diagnostic tests. In addition to the domination on the domestic market, Russian diagnostic companies could also consider to extend their diagnostic solutions, potentially through franchise networks, onto the markets of low-income countries. The biobanks of STI samples could be established. Global biotechnological manufacturers could apply novel technologies in the areas and on clinical specimen previously not investigated.

Policy makers

Fourth, policy makers could consider to implement revised STI control and cancer prevention strategies, which would include the educational programmes on prevention and importance of early detection of STI across the nation, lack the stigma on sexual minorities, importance of collaboration and sharing knowledge, implementation of cervical screening and HPV vaccination programmes. This should also result in improvement of case reporting and surveillance systems, obtaining reliable epidemiological data in the country on Ct, HPV and other STI, including HIV, to better control of STI.

Translation and innovation

The results of this thesis could contribute to the translation of research into process, product, and eventually more research.

Process

The current findings on Ct prevalence in Russia give an opportunity for the development and introduction of Chlamydia screening programmes among high-risk populations in the

country. The results of this thesis inform healthcare policy makers regarding on which populations such programmes could apply and which diagnostic approaches could be used, including tests and anatomical sites to be sampled (**Chapter 2**).

An improved systematic and comprehensive surveillance and control system, obtained through a joint participation of all parties involved on the regional and federal levels, would be suitable to identify the real incidence of Ct and other STI infections, including HIV, potentially monitor diagnostic and treatment failures and collect data on microbiological characteristics of STI and the scale of antibacterial resistance. Improved knowledge about the distribution of these STI will move the public health agenda towards better STI and HIV prevention and treatment programmes that would result in developing and promoting educational campaigns, reducing stigma and approaching the populations of the great need across the nation. An improved subsequent control of STI will also save costs for the public health system, as it will reduce long-term complications, potentially decrease HIV transmission, and moreover decrease healthy life years lost by improving physical, psychological, and sexual health. On the global scale, understanding of reasons for global diversification of Ct strain types, obtained through collecting and sequencing Chlamydia-positive samples within screening and improved diagnostic programmes in Russia will improve knowledge on the natural history of Ct, decipher transmission patterns of the bacterium and, potentially, treatment failure (as described in **Chapter 3**).

The first national data on HPV prevalence in the anal canal among a male population that included MSW and MSM of a diverse HIV status (**Chapters 7 and 8**) should be extended with the studies among the general population, including different anatomical sites, to obtain the national data on HPV prevalence in men and women with anal and in women with cervical intraepithelial neoplasia, as a baseline for surveillance of the vaccination program. This will help to move the public health agenda towards organized HPV-based cervical cancer screening in women and gender-neutral HPV vaccination programmes as cost-effective, priority cancer prevention strategy.

Products

The thesis proposes several product decisions that could be of great interest for clinicians, public health specialists and policy makers in Russia and worldwide.

First, the studies in the thesis stress the importance of establishment of national biobanking programmes. Clinical significance of diversity in Ct variants between Russia

and other geographic regions, observed abundance of HPV types detected in prostate secretion and anal specimens and their role in cancerogenesis, or further studies on the microbiome will request such large and geographically diverse collection of clinical samples. Second, the thesis invites the (local) industry to (further) develop and introduce accurate and rapid molecular point-of-care tests in the world of STI, in particular Ct and HIV. Third, more accurate (than based on the detection of HPV DNA) diagnostic approaches that could allow to distinguish between new or persistent HPV infection will have great health benefits compared to the classical diagnostic approach and can be implemented not only for HPV epidemiology and transmission studies but also in cancer prevention strategies.

Research

The thesis provides research leading to answers, but also leading to more questions.

- Available data on the epidemiology of Ct and other STI, including HIV, in Russia remain limited. National reports on STI exist but the case reporting and STI surveillance system, including compulsory partner notification and tracing are needed to be improved. Little if any Ct studies have been performed among established high-risk populations (MSM, female sex workers, etc.). No studies on potentially present LGV infections among high-risk populations have been done. The diagnostics of Ct remain suboptimal in many places. More research is needed to estimate the real figures on epidemiology of Ct and other STI in Russia.
- There are some geographic variations in Chlamydia strains between different geographic areas (e.g. between Russia and Europe, Europe and Americas). More additional research is needed to elucidate potentially existing selective pressure and/or adaptive diversification in different regions worldwide and the reasons behind that.
- The access to antibiotics in Russia is regulated but self-medication practices are common due to the ongoing non-prescription access to antimicrobials and popular self-prescribing. As inadequate treatment may result in short and long term complications, more research is needed to estimate the scale of the problem.
- Data on the prevalence of genital HPV infection in Russia is geographically narrow and remain limited with the cervix. The number of national studies on the

relationships between HPV and cancer is scarce. National studies on the relationships between HPV and anal cancer among high-risk populations are lacking. More research is needed to estimate the epidemiology of HPV in Russia, including among high-risk populations.

- Studies among sexual minorities are limited and complicated due to social stigma. Implementation research especially focused on interventions for STI prevention and point-of-care approaches to disease diagnosis, including qualitative research on issues such as stigma, is needed.
- There is no organized HPV vaccination programme in Russia. To launch educational campaigns for successful HPV vaccination programmes, research on how the population and professionals in the country would accept HPV vaccines would be recommended.
- Many microorganisms are continuously threatening to infect the human urogenital tract (including prostate) and (also) anal canal, but their virulence is balanced by host-protective mechanisms. The further molecular and genomic studies are needed to elucidate whether transmitted STI or harbouring (non-)viral infections are involved in genital and anal carcinogenesis in both men and women, to analyse the potential protective and causative role of microbiome.
- The presence of HPV DNA does not necessarily indicate the presence of infectious virus. It is also important to study whether HPVs detected in the anal canal in MSW by PCR-based technology are viable and have clinical consequences. Further studies might also explain transmission of HPV types among men and to their (sexual) partners, the tissue tropism and role of cutaneous HPVs in anal disorders.
- Ongoing modelling and cost-effectiveness studies relevant to STI are narrow geographically but lacking in Russia. To better addressing STI prevention and treatment interventions, further studies should focus on these aspects.

These key points above should be focus of further research, with the potential to provide clinical practice and public health specialists and policy makers with relevant data on the two most common bacterial and viral STI worldwide, to give further guidance towards better STI control and cancer prevention strategies.